

1. (Currently amended) A [[L]] liquid pharmaceutical formulation for the prolonged release of active principle(s) (AP), ~~this said~~ formulation comprising an aqueous colloidal suspension of low viscosity based on submicronic particles of water-soluble biodegradable polymer [PO] ~~[[PO]]~~ carrying hydrophobic groups [HG] ~~[[HG]]~~, said submicronic particles being non-covalently associated with at least one active principle (AP), wherein characterized in that:

~~[[the]]~~ a dispersion medium of the suspension comprises ~~consists essentially of~~ water~~[[,]]~~;

~~said formulation is capable of being injected parenterally and~~
said formulation forms then forming a gelled deposit *in vivo* when injected parenterally and this formation of a gelled deposit~~[[,]]~~ ;

~~on the one hand being wherein said formulation is~~ at least partly caused by at least one physiological protein present *in vivo*~~[[,]]~~ ;

~~and on the other hand making it possible to prolongs and controls the~~ *in vivo* release time of the AP beyond 24 h after administration~~[[,]]~~ ;

~~[[it]]~~ is liquid under the injection conditions~~[[,]]~~ ;

and ~~[[it]]~~ is ~~[[also]]~~ liquid at the physiological temperature and/or at the physiological pH and/or in the presence of:

a physiological electrolyte in a physiological concentration,
and/or at least one surfactant.

2. (Currently amended) [[F]] The formulation according to claim 1, characterized in that its concentration of [PO] is set at a ~~sufficiently high to~~ value that allows the formation of a gelled deposit *in vivo* after parenteral injection, in the presence of at least one physiological protein.

3. (Currently amended) A [[L]] liquid pharmaceutical formulation for the prolonged release of active principle(s) (AP), this formulation:

a) being liquid in the ambient atmosphere~~[[,]]~~ ;

b) ~~[[also]]~~ being liquid at the physiological temperature and/or at the physiological pH and/or in the presence of:

a physiological electrolyte in a physiological concentration,

and/or at least one surfactant[[,]] ;

c) and comprising an aqueous colloidal suspension of low viscosity based on submicronic particles of water-soluble biodegradable polymer [PO] carrying hydrophobic groups [HG], said particles being non-covalently associated with at least one active principle AP, and the dispersion medium of the suspension comprises ~~consisting essentially of~~ water, characterized in that its concentration of [PO] is set at a ~~sufficiently high to~~ value that allows the formation of a gelled deposit *in vitro*, in the presence of at least one protein.

4. (Currently amended) [[F]] The formulation according to claim 1, ~~any one of the preceding claims, characterized in that its~~ wherein the concentration of [PO] is ~~such that:~~

$[PO] \geq 0.9.C1,$

~~preferably~~ $20.C1 \geq [PO] \geq C1,$

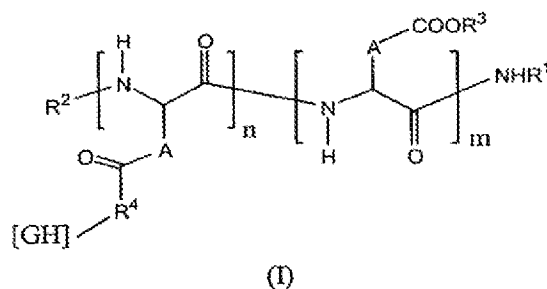
~~and particularly preferably~~ $10.C1 \geq [PO] \geq C1,$

where C1 is the “induced gelling” concentration of the particles of PO, as measured in an IG test.

5. (Currently amended) [[F]] The formulation according to claim 1 ~~any one of the preceding claims, characterized in that its~~ wherein said formulation has a viscosity [[is]] less than or equal to 5 Pa.s.

6. (Currently amended) [[F]] The formulation according to claim 1 ~~any one of the preceding claims, characterized in that~~ wherein the polymer [PO] is a polyamino acid formed of aspartic units and/or glutamic units, at least one of said ~~some of these~~ units carrying grafts containing at least one hydrophobic group [HG] ~~[[HG]]~~.

7. (Currently amended) [[F]] The formulation according to claim 6, characterized in that the [PO] is ~~[[are]]~~ defined by general formula (I) below:



in which:

R^1 is selected from the group consisting of: H, a linear C2 to C10 alkyl or branched C3 to C10 alkyl, benzyl, a terminal amino acid unit and $[[\text{or}]] -R^4-[HG]$;

R^2 is selected from the group consisting of: H, a linear C2 to C10 acyl or branched C3 to C10 acyl group, a pyroglutamate and $[[\text{or}]] -R^4-[HG]$;

R^3 is selected from the group consisting of: H and $[[\text{or}]]$ a cationic entity ~~preferably~~ selected from the group consisting of comprising:

metal cations ~~advantageously~~ selected from the subgroup consisting of comprising sodium, potassium, calcium and magnesium,
 organic cations ~~advantageously~~ selected from the subgroup consisting of comprising:
 cations based on amine,
 cations based on oligoamine,
 cations based on polyamine (~~polyethylenimine being particularly preferred~~), and
 cations based on amino acid(s) ~~advantageously~~ selected from the class consisting of comprising: cations based on lysine or arginine,
 and cationic polyamino acids ~~advantageously~~ selected from the subgroup comprising polylysine and oligolysine;

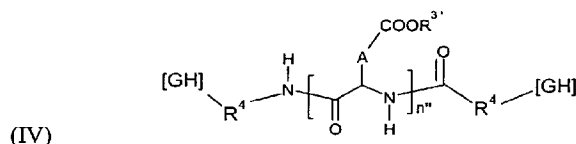
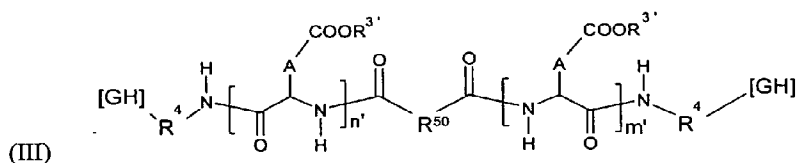
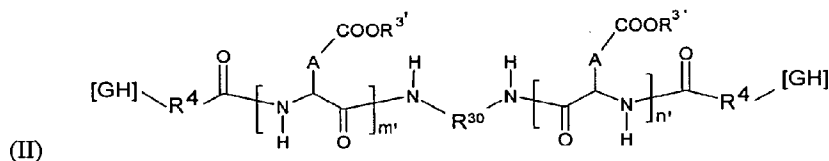
R^4 is a direct bond or a spacer based on 1 to 4 amino acid units;

A independently is a radical $-\text{CH}_2-$ (~~aspartic unit~~) or $-\text{CH}_2-\text{CH}_2-$ (~~glutamic unit~~);

$n/(n+m)$ is defined as the molar grafting rate and its value is sufficiently low for [PO], dissolved in water at pH 7 and at 25°C, to form a colloidal suspension of submicronic particles of [PO], ~~$n/(n+m)$ preferably being between 1 and 25 mol % and particularly preferably between 1 and 15 mol %;~~

$n + m$ varies from 10 to 1000 and ~~preferably between 50 and 300~~;
 [HG] is a hydrophobic group.

8. (Currently amended) [[F]] The formulation according to claim 6, characterized in that the [PO] has ~~(have)~~ one of general formulae (II), (III) and (IV) below:



in which:

[HG] is a hydrophobic group;

R^{30} is a linear C2 to C6 alkyl group;

$R^{3'}$ is H or a cationic entity ~~preferably~~ selected from the group comprising:

metal cations ~~advantageously~~ selected from the subgroup ~~comprising~~ consisting of sodium, potassium, calcium and magnesium,

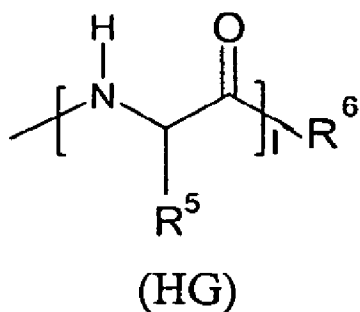
organic cations ~~advantageously~~ selected from the subgroup ~~comprising~~ consisting of: cations based on amine, cations based on oligoamine, cations based on polyamine (~~polyethylenimine being particularly preferred~~), and cations based on amino acid(s) ~~advantageously~~ selected from the class comprising cations based on lysine or arginine, and cationic polyamino acids ~~advantageously~~ selected from the subgroup comprising polylysine and oligolysine;

R^{50} is a C2 to C6 alkyl, dialkoxy or diamine group;

R^4 is a direct bond or a "spacer" based on 1 to 4 amino acid units;

A independently is a radical $-\text{CH}_2-$ (~~aspartic unit~~) or $-\text{CH}_2\text{CH}_2-$ (~~glutamic unit~~);
 $n' + m'$ or n' is defined as the degree of polymerization and varies from 10 to 1000
~~and preferably between 50 and 300.~~

9. (Currently amended) ~~[[F]]~~ The formulation according to claim 7 ~~[[or 8]]~~,
characterized in that the [HG] of the [PO] each independently of one another are a monovalent
radical of the formula below:



in which:

R^5 is a methyl (~~alanine~~), isopropyl (~~valine~~), isobutyl (~~leucine~~), sec-butyl
(~~isoleucine~~) or benzyl (~~phenylalanine~~);

R^6 is a hydrophobic radical containing from 6 to 30 carbon atoms;

l varies from 0 to 6.

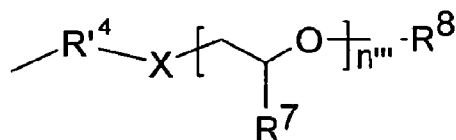
10. (Currently amended) ~~[[F]]~~ The formulation according to claim 9, ~~characterized in~~
~~that all or some of~~ wherein at least one of the hydrophobic radicals R^6 of the [PO] ~~[[are]]~~ is
independently selected from the group of radicals ~~comprising~~ consisting of:

a linear or branched alkoxy containing from 6 to 30 carbon atoms and ~~optionally~~
~~of~~ containing at least one heteroatom (~~preferably O and/or N and/or S~~) and/or at least one unit of
unsaturation,

an alkoxy containing 6 to 30 carbon atoms, having one or more fused carbocyclic
rings and ~~optionally~~ containing at least one unit of unsaturation and/or at least one heteroatom
(~~preferably O and/or N and/or S~~),

an alkoxyaryl or an aryloxyalkyl having 7 to 30 carbon atoms and capable of
containing at least one unit of unsaturation and/or at least one heteroatom (~~preferably O and/or N~~
~~and/or S~~).

11. (Currently amended) ~~[[F]]~~ The formulation according to claim 9 ~~[[or 10]]~~, ~~characterized in that all or some of~~ wherein the hydrophobic radical R⁶ of the graft of the [PO] is derived from an alcohol precursor selected from the group ~~comprising~~ consisting of: octanol, dodecanol, tetradecanol, hexadecanol, octadecanol, oleyl alcohol, tocopherol and cholesterol.
12. (Currently amended) ~~[[F]]~~ The formulation according to claim 6, characterized in that the [PO] ~~consists~~ comprises of an alpha-L-glutamate or alpha-L-glutamic homopolymer.
13. (Currently amended) ~~[[F]]~~ The formulation according to claim 6, ~~characterized in that wherein~~ the [PO] ~~consists~~ comprises of an alpha-L-aspartate or alpha-L-aspartic homopolymer.
14. (Currently amended) ~~[[F]]~~ The formulation according to claim 6, ~~characterized in that wherein~~ the [PO] ~~consists~~ comprises of an alpha-L-aspartate/alpha-L-glutamate or alpha-L-aspartic/alpha-L-glutamic copolymer.
15. (Currently amended) ~~[[F]]~~ The formulation according to claim 14, ~~characterized in that wherein~~, in the [PO], the distribution of the aspartic and/or glutamic units carrying grafts containing at least one [HG] unit is such that the resulting polymer is either random or of the block type or of the multiblock type.
16. (Currently amended) ~~[[F]]~~ The formulation according to claim 1, ~~characterized in that wherein~~ the molecular weight of the [PO] is between 2000 and 100,000 g/mol ~~and preferably between 5000 and 40,000 g/mol~~.
17. (Currently amended) ~~[[F]]~~ The formulation according to claim 6, ~~characterized in that wherein~~ the [PO] carries at least one graft of the polyalkylene glycol type bonded to a glutamate and/or aspartate unit.
18. (Currently amended) ~~[[F]]~~ The formulation according to claim 17, ~~characterized in that wherein~~ the graft of the polyalkylene glycol type has formula (V) below:



(V)

in which:

R⁴ is a direct bond or a "spacer" based on 1 to 4 amino acid units;

X is a heteroatom selected from the group ~~comprising~~ consisting of: oxygen, nitrogen and sulfur;

R⁷ and R⁸ independently are H or a linear C1 to C4 alkyl;

n''' varies from 10 to 1000 ~~and preferably from 50 to 300~~.

19. (Currently amended) ~~[[F]] The formulation according to claim 17 [[or 18]], characterized in that~~ wherein the polyalkylene glycol is a polyethylene glycol.

20. (Currently amended) ~~[[F]] The formulation according to any one of claim [[s]] 17 [[to 19]], characterized in that~~ wherein the molar percentage of polyalkylene glycol grafting varies from 1 to 30%.

21. (Currently amended) ~~[[F]] The formulation according to claim 1 wherein any one of claims 1 to 20, characterized in that~~ the hydrophobically modified polymers [PO] are selected from the group ~~comprising~~ consisting of: polyamino acids, polysaccharides (~~preferably those in the subgroup comprising pullulans and/or chitosans and/or mucopolysaccharides~~), gelatins and mixtures thereof.

22. (Currently amended) ~~[[F]] The formulation according to claim 1, wherein any one of the preceding claims, characterized in that~~ the AP is selected from the group consisting of: a protein, a glycoprotein, a protein bonded to one or more polyalkylene glycol chains [~~preferably polyethylene glycol (PEG) chains: "PEGylated protein"~~], a polysaccharide, a liposaccharide, an oligonucleotide, a polynucleotide ~~[[or]] and~~ a peptide, ~~said AP preferably being selected from haemoglobins, cytochromes, albumins, interferons, cytokines, antigens,~~

~~antibodies, erythropoietin, insulin, growth hormones, factors γ m and IX, interleukins or mixtures thereof, and haemopoiesis stimulating factors.~~

23. (Currently amended) ~~[[F]]~~ The formulation according to claim 1, wherein ~~any~~
~~one of claims 1 to 21, characterized in that the active principle AP is a “small” hydrophobic,~~
hydrophilic or amphiphilic organic molecule.

24. (Currently amended) ~~[[F]]~~ The formulation according to claim 1, wherein ~~any~~
~~one of claims 1 to 22, characterized in that it's the weight fraction of AP not associated with the~~
submicronic particles [non-associated AP], in weight %, is such that:

$$[\text{non-associated AP}] \leq 1, \text{ preferably } [\text{non-associated AP}] \leq 0.5.$$

25. (Currently amended) ~~[[F]]~~ The formulation according to claim 1 wherein ~~any one~~
~~of the preceding claims, characterized in that it the formulation~~ is injectable by the parenteral,
subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour.

26. (Currently amended) ~~[[F]]~~ The formulation according to claim 1 wherein ~~any one~~
~~of the preceding claims, characterized in that it the formulation~~ is intended for the preparation of
used to prepare drugs, particularly for administration by the parenteral, subcutaneous,
intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour, or by the oral,
nasal, vaginal or ocular route.

27. (Withdrawn -- Currently amended) Process for the preparation of drugs,
particularly for administration by the parenteral, subcutaneous, intramuscular, intradermal,
intraperitoneal or intracerebral route or into a tumour, or by the oral, nasal, vaginal or ocular
route, ~~characterized in that it consists essentially in using~~ comprising at least one formulation
according to ~~any one of claim~~ ~~[[s]] 1~~ ~~[[to 26]]~~.

28. (Currently amended) A ~~[[D]]~~ derived product, ~~characterized in that it comprises~~
comprising submicronic particles formed of non-covalent PO/AP associations as defined in
claim 1, and ~~in that it is~~ obtained from the formulation according to ~~any one of claim~~ ~~[[s]] 1~~ ~~[[to~~
~~26]]~~.

29. (Currently amended) The [[D]] derived product according to claim 28, ~~said product is in~~ characterized in that it consists of a powder or a gel ~~form~~.

30. (Withdrawn -- Currently amended) A [[P]] process for the preparation of the formulation of claim 1, said process comprising the steps of: ~~according to any one of claims 1 to 26, characterized in that it consists essentially in:~~

taking a colloidal suspension of nanoparticles of at least one PO,
mixing this colloidal suspension of nanoparticles of PO with at least one AP,
~~preferably~~ in aqueous solution, and
~~optionally adding at least one excipient,~~
adjusting the pH and/or the osmolarity if necessary, ~~and~~
~~optionally filtering the resulting suspension.~~

31. (Withdrawn -- Currently amended) A [[P]] process according to claim 30, ~~characterized in that~~ wherein the at least one AP is [[(are)]] in the form of an aqueous suspension or solution for mixing with the colloidal suspension of nanoparticles of PO.

32. (Withdrawn -- Currently amended) A [[P]] process for the preparation of the formulation of claim 1, said process comprising the steps of: ~~according to any one of claims 1 to 26, characterized in that it consists essentially in:~~

taking a powder of nanoparticles of at least one PO,
mixing this powder with an aqueous suspension or solution of at least one AP,
~~preferably~~ in aqueous solution, and
~~optionally adding at least one excipient,~~
adjusting the pH and/or the osmolarity if necessary, ~~and~~
~~optionally filtering the resulting suspension.~~

33. (Withdrawn -- Currently amended) A [[P]] process for the preparation of the formulation
of claim 1, said process comprising the steps of: ~~according to any one of claims 1 to 26, characterized in that it consists essentially in:~~

taking a powder produced by drying the liquid formulation ~~according to~~
according to claim 1 ~~any one of claims 1 to 26~~,
mixing this powder with an aqueous liquid medium, ~~and preferably with stirring,~~
~~optionally adding at least one excipient,~~
adjusting the pH and/or the osmolarity if necessary, ~~and~~
~~optionally filtering the resulting suspension.~~

34. (Withdrawn -- Currently amended) A[[P]] process for the preparation of a
powder derived from the formulation of claim 1, wherein ~~according to any one of claims 1 to 26,~~
~~characterized in that~~ said powder is obtained by drying the formulation of claim 1 ~~according to~~
~~any one of claims 1 to 26.~~